UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,627	04/14/2004	Renata Pasqualini	UTSC:858US	6275

32425 7590 12/08/2006

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/824,627	PASQUALINI ET AL.
	Examiner	Art Unit
	Ileana Popa	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,9-16,18,21-23 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9-16,18,21-23 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/06/2006 has been entered.

2. In the submission filed on 09/06/2006, claim 2 was amended. No new matter was introduced by the amendment. Claims 1, 8, 17, 19, 20, 24, and 39 have been cancelled.

Claims 2-7, 9-16, 18, 21-23, and 25-38 are pending and under examination.

Note: Change of Examiner

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

> matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 2-7, 9-16, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow et al. (Antibodies: A Laboratory Manual, 1988, of record), in view of Jat et al. (Proc Natl Acad Sci USA, 1991, 88: 5096-5100, of record), Kano (JP62195296, of record), and Kanki (Hybridoma, 1994, 13: 327-330, of record) for the reasons of record set forth in the prior Office action.

Applicants assert that the Examiner did not establish a *prima facie* case. Applicants argue that Harlow et al. teach traditional monoclonal antibody preparation, using hybridoma formation and therefore, they teach against the present invention, which is drawn to preparation of monoclonal antibodies without the need of hybridoma formation. Applicants submit that Harlow et al. teach that, in order to prepare monoclonal antibodies, formation of hybridoma is an absolute requirement and therefore the reference does not leave open any other possibilities. Applicant argues that, although the Examiner implies that Harlow et al. do not necessarily require hybridoma formation, he fails to point any specific teaching in the reference to support this position. Regarding Jat et al., Applicants argue that the reference provides no suggestion for using the Immortomouse in the preparation of monoclonal antibodies and that the Examiner relies on statement from Jat et al. that is irrelevant to the present invention because it says nothing about using antibody-producing cells from the Immortomouse to produce monoclonal antibodies. The Applicants submit that the statement from Jat et al. merely says "other cell systems" without reference for any

particular cell type. Regarding Kano and Kanki, Applicants argue that they clearly teach away from the present invention because they teach the use of oncogene to prepare transgenic, immortalized B-cells cultures *ex vivo*, as opposed to the present invention that does the opposite, i.e., the already antigen-primed B-cells have the ability to be immortalized and there is no requirement of transforming the B-cells *in vitro*. Applicants submit that this is an important improvement because the efficiency is higher and the process is less complicated. Applicants continue arguing that Kano and Kanki are not combinable with Harlow et al. because Harlow et al. teach a different approach, i.e., to remove antigen-primed B-cells and immortalize them by fusing them with myeloma to form a hybridoma. Applicants assert that, even if these references were to be combined, such a combination would teach away from the present invention because such a combination would teach to take the antibody-secreting cells of Harlow et al. and immortalize them *ex vivo*, as taught by Kano and Kanki. Applicants assert that there would be no need or motivation for one of skill in the art to employ an alternative approach and use the conditionally immortal cells of the Immortomouse taught by Jat et al., especially that they don't specifically teach that this mouse can be used for monoclonal antibody production. Finally, Applicants argue that, upon viewing Harlow, there is simply no evidence of a problem to be solved and therefore it is improper to conclude that an invention is obvious absent evidence that one of skill in the art would have recognized that an underlying problem existed.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that Harlow et al. teach that formation of hybridoma is an absolute requirement and therefore they do not leave open any other possibilities is inaccurate. Nowhere in the citation from Harlow et al. is any such requirement made. Further, Applicants did not point out where Harlow et al. make this statement. Harlow et al. teach hybridoma only as means to immortalize antigen-primed B-cells in order to obtain cell lines producing monoclonal antibodies of interest. This does not mean that other immortalization procedures do not exist. On the contrary, the prior art teaches other means of immortalizing B-cells for the production of antibodies. Kanki teaches immortalization of human primary B-cells (i.e., antigen-primed) by using the SV40 T antigen, wherein the cells are capable of producing antibodies, and also that this technique could be used to develop cell lines secreting human monoclonal antibodies, without the need of forming hybridoma (Abstract, p. 327, column 1 and 2, p. column 1, last paragraph). Kano teaches the use of SV40 DNA to immortalize antigen-primed splenocytes for the production of stable monoclonal antibody-producing B-cells, without the need of forming hybridoma (Abstract). Clearly the art teaches direct immortalization of B-cells using oncogenes such as the SV40 T antigen as an alternative approach to generate immortalized B-cell lines for the production of monoclonal antibodies. One of skill in the art would readily recognize the utility of such approaches, especially that Harlow et al. recognizes problems with the use of hybridoma as means for immortalization (see the passage quoted by the Applicant on p. 8 of the response to the

Office action filed on 09/06/2006, which states that "hybridoma production seldom takes less than 2 months from start to finish, and it can take well over a year". Therefore, one of skill in the art would recognize the existence of a problem to be solved and would be motivated to circumvent the need for hybridoma as means to immortalize B-cells. Jat et al. teach that immortalization *ex vivo* is complex and unpredictable and that generation of the Immortomouse overcomes these because it facilitates and it ensures the presence of the conditional oncogene in all cells, at a common integration site (p. 5096, column 1 and 2). Even if they do not specify B-cells, Jat et al. clearly teach the use of Immortomouse for direct derivatization of cell lines from a wide variety of tissues and cell types (p. 5096, column 2,last paragraph, p. 5100, column 1 last paragraph). Based on all the teachings above, one of skill in the art would have been motivated to employ the alternative approach of using conditionally immortalized B-cells obtained from the Immortomouse of Jat et al. One of skill in the art would readily recognize this as being a straightforward method to produce monoclonal antibodies in the absence of hybridoma formation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

5. Claims 2-7, 9-16, 18, 21-23, and 25-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow et al. taken with Jat et al., Kano, and Kanki, as applied to claims 2-7, 9-16, 21-23, in further view of Green (J Immunol Meth, 1999, 231: 11-23, of record), for the reasons of record set forth in the prior Office actions.

Applicants assert that the Examiner did not establish a *prima facie* case. Applicants argue that Green simply describes the use of the Xenomouse to produce human antibodies, but he does not teach or suggest a Xenomouse that has antibody-producing cells comprising a pre-existing oncogene that renders them capable of being immortalized. Applicants argue that, to arrive to such a teaching, one of skill in the art would have to postulate the cross-breeding of the Xenomouse with the Immortomouse and that the cited prior art does not teach or suggest this. Applicants argue that the Examiner fails to identify any specific teaching within either Jat et al. or Green that would motivate one of skill in the art to cross the mouse of Green with the mouse of Jat et al. and that there is no reason for the Examiner to conclude that it would have been obvious to make such a cross.

In response to applicant's argument that there is no teaching or to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Green teaches that, although mice are convenient for immunization and therapeutic monoclonal antibodies against human antigens have been of murine origin, murine antibodies have inherent disadvantages as human therapeutics (p. 12, column 1). Green teaches the Xenomouse, which allows for the production of human antibodies from a mouse,

wherein the antibodies lacking immunogenicity in humans (p. 12, column 2, first full paragraph, p. 13, column 1, second and third paragraphs, p. 20, columns 1 and 2). Although Green does not teach the cross between the Xenomouse and the Immunomouse, he teaches the use of the Xenomouse in conjunction with well-established hybridoma procedures (i.e., immortalization) to produce human monoclonal antibodies (p. 13, column 2, p. 18, column 1, first full paragraph, p. 21, column 1 bridging column 2). Therefore, like Harlow et al., Green teaches the need to immortalize the antigen-primed B-cell to obtain cell lines secreting the monoclonal antibody of interest. Green also teaches that the Xenomouse offers flexibility, allowing the production of monoclonal antibodies either directly from hybridoma, from recombinant cell lines, or from transgenic animals (p. 19, column 2, second full paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to immortalize the B-cell of the Xenomouse by crossing it with the Immortomouse to obtain a transgenic animal whose B-cells express both the conditional transforming oncogene and the genetic complement for human antibody production, with a reasonable expectation of success. For motivation, see above. One of skill in the art would have been expected to have a reasonable expectation of success because such crossing procedures are routine in the art.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

7. Claims 15 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claims 15 and 34 recite the broad recitations “proteins”, “pathogenic microorganisms”, “tissue”, “whole cells, “subcellular components”, and the claim also recites “peptides”, “glycoproteins”, “lipoproteins”, “purified proteins, “partially purified proteins”, “bacteria”, “fresh or cultured tissue”, “laser captured tissue”, paraffin

embedded and fixed tissue", "patient-derived cells", "fresh or cultured cells", "membrane" and "cytoplasm", respectively, which are the narrower statements of the ranges/limitations.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER